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LETTERS AND CORRESPONDENCE

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Very Severe Aplastic Anemia Following Resection of Lymphocytic Thymoma: Effectiveness of Antilymphocyte Globulin, Cyclosporin A, and Granulocyte-Colony Stimulating Factor

To the Editor: Aplastic anemia (AA) is a very uncommon complication of thymoma and is extremely infrequent following the surgical removal of a thymic tumor [1–3]. As thymoma-associated hematological dyscrasias are supposed to be of immunologic origin [2,3], we present here a case of very severe AA following the resection of lymphocytic thymoma where the effectiveness of antilymphocyte globulin (ALG), cyclosporin A (Cyc A), and granulocyte-colony stimulating factor (G-CSF) [4] is described.

The patient M.I. was a 38-year-old male in whom widening of the mediastinum was detected by an X-ray film of the chest, performed during an upper respiratory tract infection in February 1998, and a mass was demonstrated in the anterior–superior mediastinum by a computerized tomographic study of the thorax, compatible with a thymoma. A well-capsulated mediastinal tumor was totally removed by thoracotomy. Histopathological examination revealed a lymphocytic thymoma (corticomedullary type). An initial workup then revealed no abnormal results including routine hematological examinations and a bone marrow sample. Three months later a physical examination performed for complaints of weakness and high fever revealed only purpura. A hematologic routine was as follows: Hb 5.1 g/dL; Hct 15.5%; reticulocytes 0.1%; platelets 2×10^9/L; WBC 1.2×10^9/L with 8% neutrophils, 90% lymphocytes, and 2% monocytes. A bone marrow biopsy revealed a very severe hypoplasia in all the three cell lines with over 90% fatty tissue. Lymphocyte studies showed a decreased CD4/CD8 ratio (0.44) in peripheral blood as the result of an increase in CD8+ T lymphocytes (0.594×10^9/L) and a low CD4+ count (0.264×10^9/L). Ham and sugar-water tests were negative. CD55 and CD 59 expressions on neutrophils and monocytes were normal. Only EBV-VCA IgG and anti CMV IgG were serologically positive. A cytogenetic examination of peripheral blood cells yielded a normal 46, XY male karyotype.

We administered 5 μg/kg/day G-CSF (day 1 to 90) in combination with 15 mg/kg/day horse ALG (day 1 to 5), 2 mg/kg/day methylprednisolone (Mpred) (day 1 to 5, then tapered and stopped on day +30), and 5 mg/kg/day Cy A orally (day 1 to 180). After obtaining a response we have since then continued CyA beyond 180 days with slow tapering. Complete response was achieved in the fifth month of treatment. Post-treatment peripheral blood counts were as follows: Hb 13 g/dL; Hct 39%; reticulocytes 2.2%; WBC 6.1×10^9/L, absolute neutrophil count 3.1×10^9/L; platelets 160×10^9/L (Fig. 1). A normal CD4/CD8 ratio (1.7) in peripheral blood was observed as the result of a decrease in CD8+ T lymphocytes (0.315×10^9/L) and an increase of CD4+ count (0.588×10^9/L).

Peripheral blood lymphocytes from five apparently healthy donors were cultured, and their mitotic indexes were estimated, before and after addition of the serum samples of the patient, obtained prior to treatment and two and six months following it respectively. While the mean mitotic index value was 5.54 ± 0.114% for healthy subjects the addition of the pretreatment serum sample to the culture decreased the value to 4.48 ± 0.148% ($P = 0.04$), whereas addition of post treatment serum samples exerted no significant change, the mean values being 5.58 ± 0.239% and 5.60 ± 0.339% for the second and sixth months respectively.

To our knowledge, the case presented here seems to be the third report reflecting the co-existence of AA following thymectomy [1,2].

The pathogenesis of some types of AA clearly displays an immunological basis [5]. Especially, the role of suppressor T lymphocytes is considered important in the development of AA. Similarly, AA associated with thymoma seems to be caused by the suppression of the bone marrow due to an unbalanced regulation and the inhibitory effects of T lymphocytes on BFU-E and CFU-E as demonstrated in two patients [2,3]. In our case, both

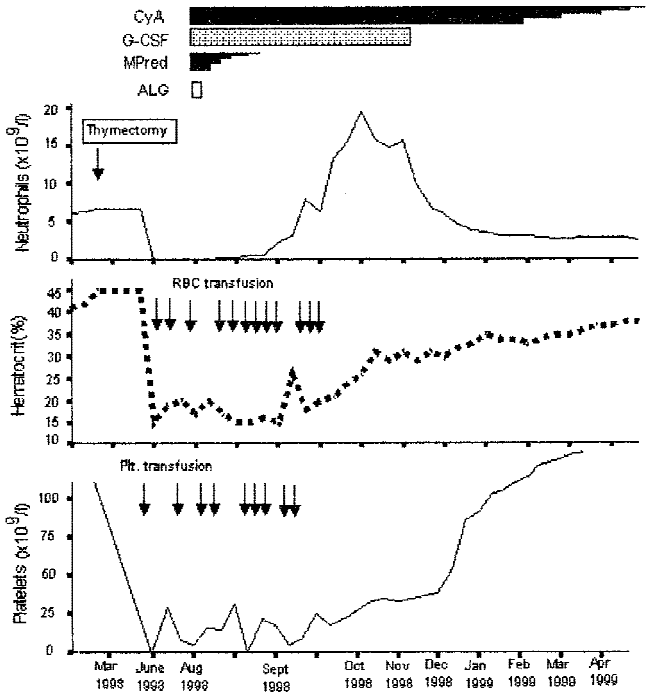

Fig. 1. Clinical course of the patient. RBC = red blood cells; PLT = platelets.

the reduced ratio of CD 4+ to CD 8^+ T cells and the inducement of a statistically significant decrease in the mitotic activity of normal lymphocytes by the addition of the patient's pretreatment serum sample to culture, plus the absence of a change in the mitotic activity, when a post-treatment serum sample was added, suggests an underlying immune mechanism. The other important finding in our patient is the complete response obtained with intense immunosuppressive treatment. This is also an indication reflecting the abolishment of the myelosuppressive mechanism, in the absence of which the medium became suitable for the multipotential stem cells to regenerate normally.

In thymoma-associated AA, immunosuppressive drugs like antithymocyte globin, Cy A, nitrogen mustard, vincristine sulfate, procarbazine, prednisolone have been used with some success [1–3]. Thus, our case seems to be an example for the development of very severe AA following surgical removal of a lymphocytic thymoma, in whom an intensive immunosuppressive protocol comprising of ALG, Cy A, and G-CSF has been highly efficient.

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Splenectomy in Thrombotic Thrombocytopenic Purpura

To the Editor: We read with great interest the paper by Mant et al. [1] on splenectomy in patients with chronic relapsing thrombotic thrombocytopenic purpura (TTP). Six of 7 patients readily recovered following splenectomy and remained in remission for at least 18 months. This observation confirms the experience of several other authors (see [2] for references) who recommended splenectomy for patients not responding to plasma therapy. The relevant pathomechanisms underlying the beneficial effect of splenectomy are considered obscure [1,2]. Our recent studies demonstrated congenital deficiency of a plasma protease, specifically cleaving von Willebrand factor (vWF), in siblings with familial TTP [3,4]. No inhibitor of vWF-cleaving protease was detected in these patients who readily responded to plasma therapy. An acquired IgG inhibitor of vWF-cleaving protease was established in a 34-year-old patient with nonfamilial TTP during his first TTP episode [5]. Remission was achieved by plasma exchange, vincristine and corticosteroid therapy, and was accompanied by transient disappearance of the inhibitor and appearance of protease activity. A first relapse of severe thrombocytopenia, preceded by disappearance of the protease, occurred 7 months after the first acute TTP event. Plasma therapy was followed by a temporary increase in the antibody titer and by recurring acute episodes of TTP. Since the patient became eventually unresponsive to plasma exchange, splenectomy was performed one year after the initial acute episode [5]. The protease inhibitor disappeared and the vWF-cleaving protease normalized, together with normalization of the platelet count. The follow-up period is now 32 months without evidence of relapses of TTP. Subsequent studies [4,6] have shown that most, if not all, patients with non-familial TTP have an acquired deficiency of vWF-cleaving protease, due to a circulating autoantibody. It is conceivable that the therapeutic effect of splenectomy is due to removal of the B cells responsible for production of inhibitor(s) of vWF-cleaving protease [5]. We believe that splenectomy should primarily be reserved for plasma refractory patients showing an antibody against vWF-cleaving protease.

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Bilateral Central Retinal Artery Occlusion Secondary to Sickle Cell Disease

To the Editor: Painful crisis is the most common complication in patients with sickle cell disease (SCD), while central retinal artery occlusion (RAO)

is rarely encountered [1]. We report a case of bilateral central retinal artery occlusion in a young patient with SCD. To our knowledge this has not been previously reported.

A 27-year-old male from Eastern Saudi Arabia with sickle cell disease, and hemoglobin (Hb) electrophoresis showing Hb S 81.4%, Hb F 13.6%, and Hb A_2 3.3% presented with vomiting, diarrhea, and sudden onset of transient dizziness and impaired vision. There was no history of smoking, alcohol, or illicit drug use. He had no history of trauma to his eyes. His general clinical examination was unremarkable except for evidence of volume depletion and jaundice. Visual acuity was limited to counting fingers at 1 foot and 2 feet on the right and left eye, respectively. Fundus examination showed congested and tortuous retinal vessels, and bilateral pale swelling of the retina. Cherry red spots were observed bilaterally.

Hb was 10.5 gm/dL, hematocrit 30.4%, WBC 15.0×10^9/L, and reticulocyte count 14.4%. Blood and stool cultures were negative. Prothrombin time, partial thromboplastin time, protein S, protein C, antithrombin III level, and homocysteine level were all normal. Test for activated protein C resistance was negative. Serologies for connective tissue diseases were negative, and C3 and C4 were normal. Electrocardiogram, Doppler echocardiography, carotid Doppler ultrasound, and magnetic resonance imaging of the brain showed no abnormalities. The patient was started on heparin, aspirin, and nifidepine. Exchange transfusion was performed, which lowered Hb S to 50%. Thrombolytic therapy was not given as the patient arrived 12 hr after the onset of symptoms. Follow-up showed mild improvement in his vision with mild neovascular formation on fundoscopy.

Thorough investigation did not reveal any underlying pathology such as hypercoagulable state, vasculitis, vascular obstruction, or source of emboli. Dehydration from diarrhea and vomiting may have caused hyperviscosity and subsequent retinal artery obstruction by sickled red blood cells. Among all the complications of SCD, RAO is not a common sequel of vaso-occlusive crisis [2]. When encountered, the occlusive process primarily involves the peripheral retina. Patients with sickle cell trait can also develop central RAO when associated with other risk factors, such as, systemic lupus erythematosis, rheumatoid arthritis, or severe dehydration [2–4]. Central RAO was estimated to occur with a frequency of 1:10,000 outpatient ophthalmology visits and is usually unilateral [1]. The major contributing factors are cardiac disease, internal carotid artery disease, vasculitis, hypercoagulable states, cigarette smoking, and diabetes mellitus [5]. In conclusion, bilateral central retinal artery occlusion is a serious event that can occur in sickle cell disease in the absence of acute painful crisis. Prompt management of dehydration may help avoid this disabling complication.

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Polycythemia in Patients Infected With Human Immunodeficiency Virus-1

To the Editor: Reports of polycythemia in association with HIV infection are rare [1–5]. We report four patients in whom polycythemia developed in association with HIV infection.

The clinical and hematological features in our patients are shown in Table I. All patients smoked cigarettes and contacted HIV infection through homosexual contact; none of the patients had splenomegaly. The results of serum vitamin B_{12} determination, hemoglobin electrophoresis, arterial blood gas analysis while breathing room air, assay of red cell 2,3 diphosphoglycerate, bone marrow biopsy, and an abdominal ultrasound were normal in all patients.

Patient 1 was diagnosed with HIV infection in 1987. He was begun on therapy with zidovudine and lamivudine in 1993. He developed cutaneous Kaposi sarcoma in 1996; his treatment was changed to stavudine, lamivudine, and indinavir and local application of retinoid gel. The lesions of Kaposi sarcoma resolved. Polycythemia was noted in 1997, and therapeutic phlebotomy was done on four occasions during 1997. Since April 1998 he has been on treatment with didanosine, nevirapine, ritonavir, and hydroxyurea, and his blood Hb concentration remains about 16 g/dL.

Patient 2 was diagnosed with acute left brachial artery occlusion associated with lupus anticoagulant and polycythemia in 1986. He was lost to follow-up except during the years 1992–1993, when he was on treatment with zidovudine; his blood hemoglobin concentration during this period ranged between 12.9 and 16 g/dL.

Patient 3 presented with oral thrush. Subsequent to his discharge he was lost to further follow-up.

Patient 4 was evaluated for polycythemia in 1981. A lymph node biopsy showed nonspecific changes. In 1983 his Hb was 20.1 g/dL; he was lost to follow-up until 1992, when he presented with oral thrush. He was not on any medications, and his Hb was 15.7 g/dL. His hemoglobin levels during 1992–1999 have ranged between 13.7 and 15.7 g/dL. He is presently on lamivudine, ritonavir, saquinavir, and zidovudine.

In two patients (patients 2 and 4) polycythemia resolved despite continued cigarette smoking; patient 1 stopped smoking for 6 months but remained polycythemic.

Battan et al. [1] reported on a patient with AIDS and polycythemia, in whom the hemoglobin normalized over 2 months; whether this was in response to antiretroviral therapy is not clear. In the patients reported by Willocks et al. [2] and Edwards et al. [3], a normal hemoglobin level was achieved within 5 months of starting therapy with zidovudine. Kennedy et al. [4] reported on a man with AIDS in whom polycythemia developed as a consequence of zidovudine therapy and responded promptly to stopping of the drug; reinstitution of zidovudine therapy resulted in a rise in the hemoglobin concentration by 3.5 g/dL in 10 weeks.

The mechanism of HIV-associated polycythemia is unknown. In vitro studies of the sensitivity of erythroid colonies to exogenous erythropoietin in patients with HIV-associated polycythemia are needed to better understand the nature of polycythemia in these patients.

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TABLE I. Clinical and Laboratory Features in 4 Patients With HIV-1 Infection and Polycythemia*

Patient	Age, sex	AIDS	CD4 (*n*)	Hb (g/dL)	WBC ($\times 10^9$/L)	Platelets ($\times 10^9$/L)	O_2 sat (%)	*p*50 (mmHg)	Ep (mU/mL)	ZDV	RBC mass (mL/kg)	Remarks
1	31 yr, M	Yes	256	19.0	6.8	189	96.0	24.0	16	No	ND	1 cm axillary lymph node
2	30 yr, M	No	451	19.8	5.3	244	94.6	28.0	ND	No	37.1	Diffuse lymphadenopathy
3	27 yr, M	No	416	21.6	8.7	179	96.0	26.5	ND	No	49.7	Diffuse lymphadenopathy
4	25 yr, M	No	398	19.3	3.7	181	96.5	24.0	ND	No	42.2	Diffuse lymphadenopathy

*Data at the time of the initial evaluation for polycythemia; Abbreviations: CD4 = $CD4^+$ T-lymphocyte count; Hb = hemoglobin concentration; WBC = total white blood cell count; O_2 sat = O_2 saturation while breathing room air; *p*50 = partial pressure of oxygen at which the hemoglobin is 50% saturated; Ep = serum erythropoietin level; RBC = red blood cell; ZDV = zidovudine therapy at the time of presentation with polycythemia; ND = not done.

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